Lung Cancer UPDATES
IASLC HIGHLIGHTS
08-14 SEPTIEMBRE 2021

Iniciativa científica de:
GECP lung cancer research

LOCALLY ADVANCED DISEASE

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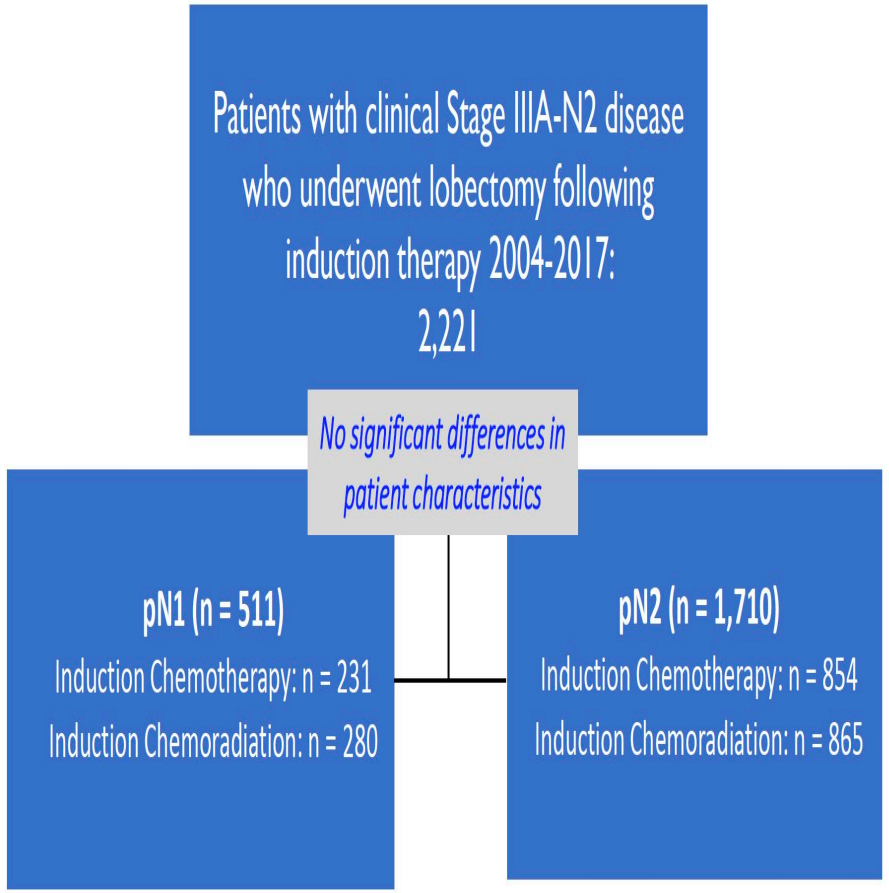
RESECTABLE STAGE III DISEASE

SURVIVAL OF PATIENTS WITH PERSISTENT N1 OR N2 DISEASE

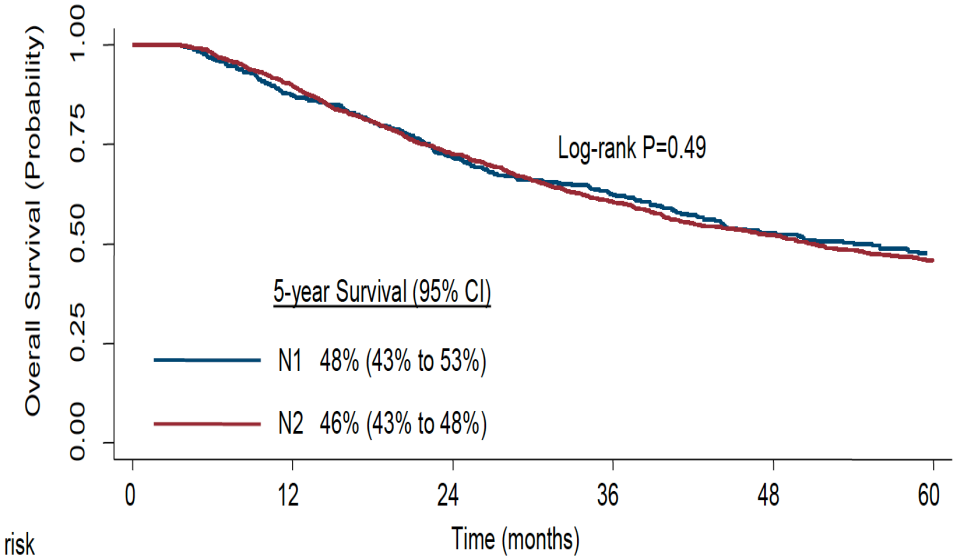
Methods

- National Cancer Data Base (NCDB)
  - Prospective database jointly sponsored by the American College of Surgeons Commission on Cancer and the American Cancer Society
- Inclusion Criteria
  - Patients with clinical T1-3 N2 M0 who underwent lobectomy after induction chemotherapy or induction chemoradiation and had pathologic N1 (pN1) or N2 (pN2) from 2004-2017
- Statistical Analysis
  - Kaplan Meier Analysis

Study Cohort

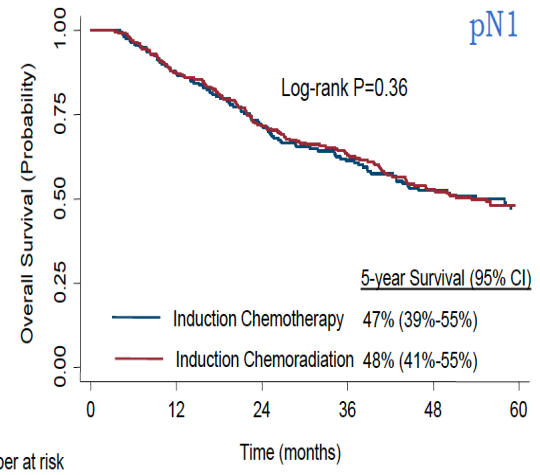


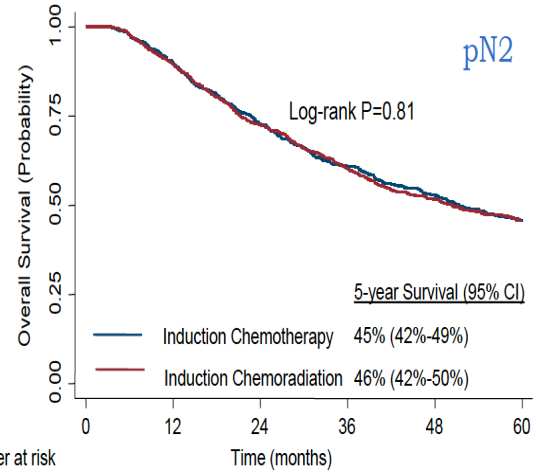
Overall Survival: Persistent N1 or N2 Disease after Induction Therapy and Lobectomy for IIIA-N2 NSCLC



Number at risk						
N1	458	396	311	237	166	121
N2	1594	1414	1096	789	584	422

No differences in Survival between Induction Chemotherapy and Induction Chemoradiation





Number at risk												
Induction Chemotherapy	201	174	137	102	70	48	Induction Chemotherapy	781	696	534	375	279	195
Induction Chemoradiation	257	222	174	135	96	73	Induction Chemoradiation	813	718	562	414	305	227

- Patients with stage IIIA-N2 NSCLC with persistent N1 and N2 after induction chemotherapy (with or without induction radiation) and lobectomy have a 5-year overall survival of 48% and 46%, respectively
- Persistent N1 and N2 disease after induction chemotherapy or induction chemoradiation for stage IIIA-N2 NSCLC should not be an absolute contraindication to surgical intervention

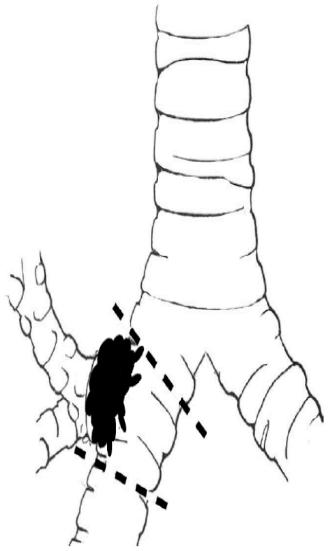
Beqari et la. OA20.04

NEOADJUVANT CHEMOTHERAPY-ALONE VS CHEMORADIATION FOLLOWED BY SLEEVE RESECTION FOR LOCALLY ADVANCED RESECTABLE NSCLC

Methods

- National Cancer Data Base (NCDB)
  - Locally advanced NSCLC treated with multi-modality therapy
  - Sleeve lung resection
  - 2006-2017
- Main exposure
  - Neoadjuvant chemotherapy-alone versus neoadjuvant chemoradiation
- Multivariable logistic regression
- Kaplan-Meier and Cox-proportional hazards

Results

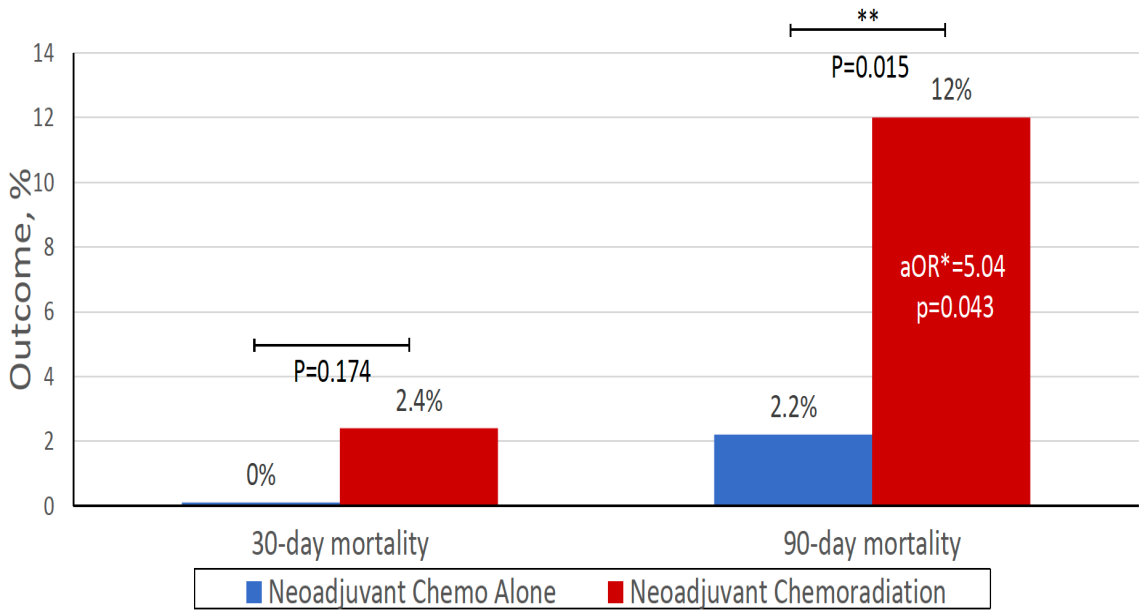


N=176 patients undergoing sleeve lung resection following

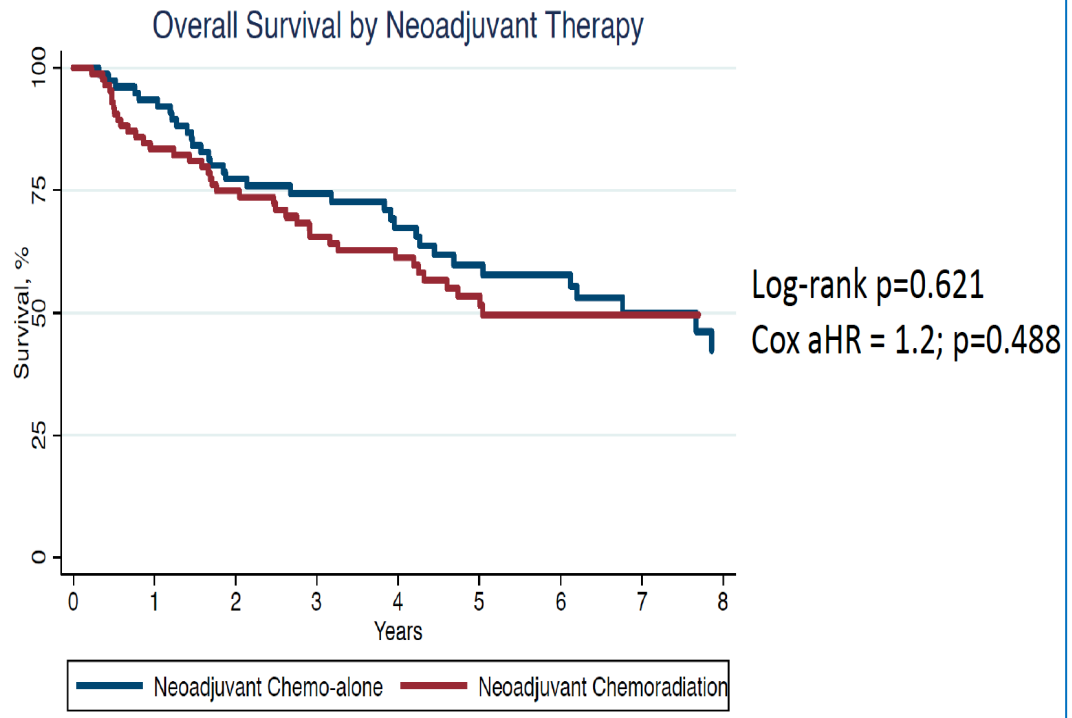
Neoadjuvant Chemotherapy-alone n=84 (47.7%)

Neoadjuvant Chemoradiation n=92 (52.3%)

Increased Mortality with Neoadjuvant Chemoradiation prior to Sleeve Lung Resection



No Difference in Overall Survival

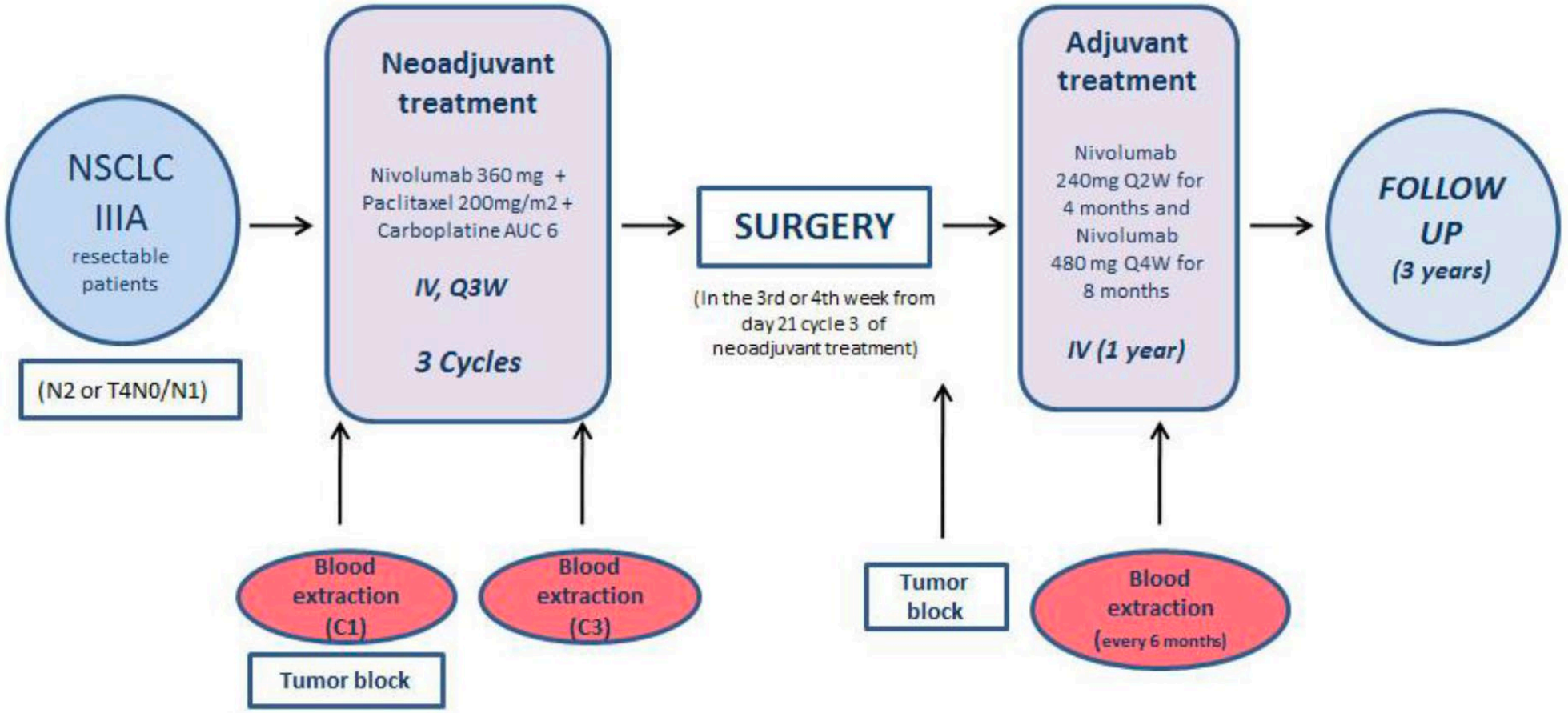


- Largest national study
- Practice patterns are nearly 50:50
- Increased mortality at 90 days with neoadjuvant chemoradiation
- No difference in margin positivity rate, but slightly higher ypCRwith chemoradiation
- No difference in overall survival
- Neoadjuvant chemotherapy alone in patients requiring a sleeve lung resection may be safer and does not jeopardize oncologic outcomes

Jaradeb M, et al. OA20.05

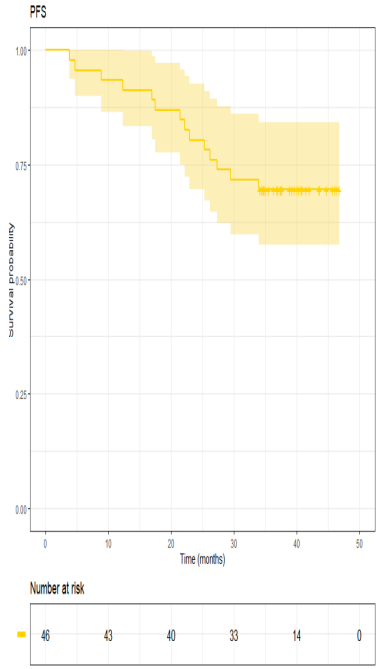
LONG TERM SURVIVAL IN OPERABLE STAGE IIIA NSCLC PATIENTS TREATED WITH NEOADJUVANT NIVOLUMAB PLUS CHEMOTHERAPY - NADIM STUDY

NADIM: Study design & Flow-chart



Provencio M, et al OA20.01

RESULTS: PFS



ITT population:

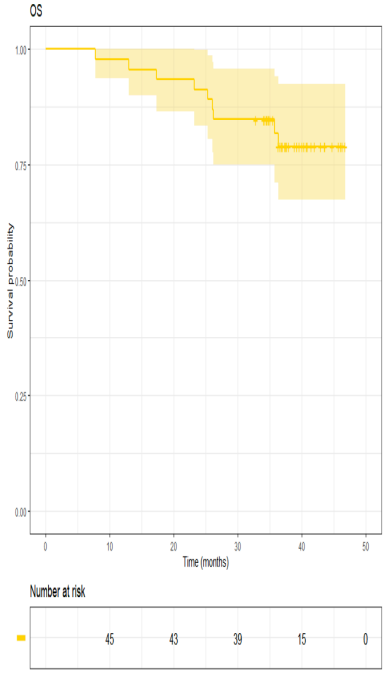
- **PFS 69.6%** (95%CI: 54.1-80.7%) **at 36 and 42 months.**

PP population:

- **PFS 81.1%** (95%CI: 64.4-90.5%) **at 36 and 42 months.**

The median PFS for patients who had progressive disease was 21.4 months (95% CI: 8.8–26.2 months)

RESULTS: OS



ITT population:

- **OS 81.9%** (95% CI: 66.8-90.6%) **at 36 months.**
- **OS 78.9%** (95%CI: 63.1-88.6%) **at 42 months.**

PP population:

- **OS 91.0%** (95%CI: 74.2-97.0%) **at 36 months.**
- **OS 87.3%** (95%CI: 69.3-95.1%) **at 42 months.**

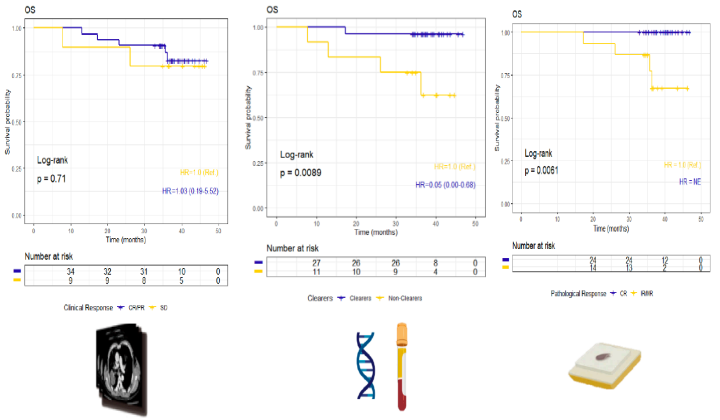
Survival surrogate	*HR (PFS)*	*95% CI*	*P*	*Adjusted PFS C-statistic*	*95% CI*	*HR (OS)*	*95% CI*	*P*	*Adjusted OS C-statistic*	*95% CI*
Clinical respone (CR+PR vs SD)	0.93	0.24-3.56	0.921	0.61	0.45-0.78	1.03	0.19-5.52	0.974	0.68	0.44-0.93
Pathological response (Complete vs Major+Incomplete)	0.25	0.06-1.00	**0.05**	0.68	0.52-0.84	--	--	--	0.83	0.75-0.91
ctDNA Clearance	0.3	0.08-1.11	**0.072**	0.62	0.43-0.81	0.05	0.00-0.68	**0.024**	0.79	0.55-1.03

MOLECULAR RESPONSE

Clearers

Non-clearers

ctDNA clearance (i.e lack of detectable ctDNA at the end of neoadjuvant tx), **significantly predicted long-term survival.**

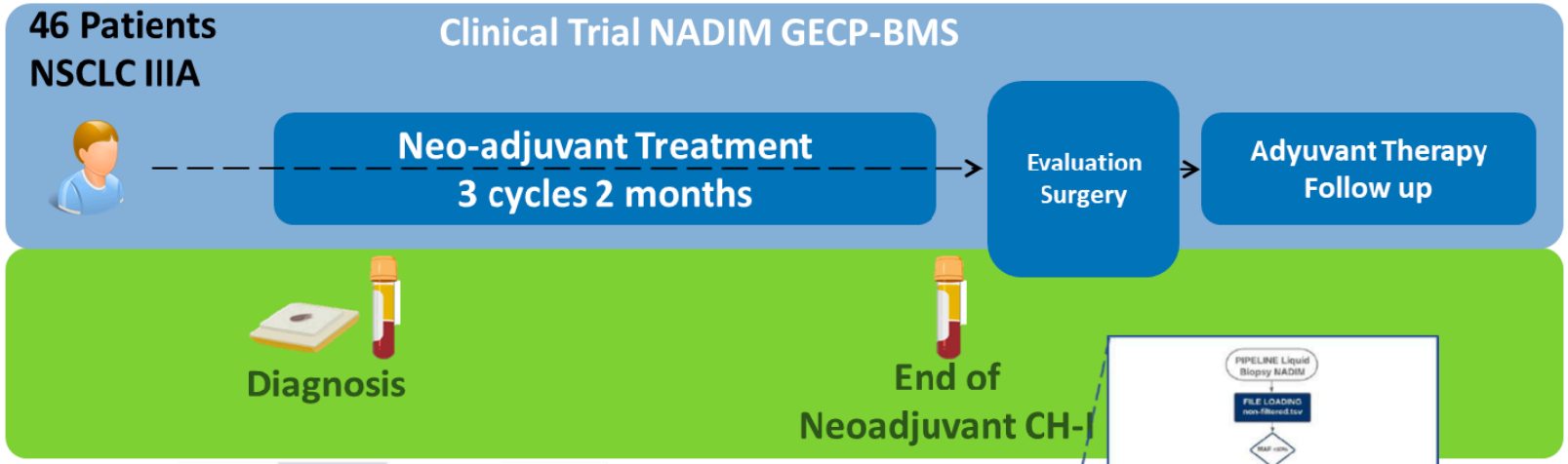


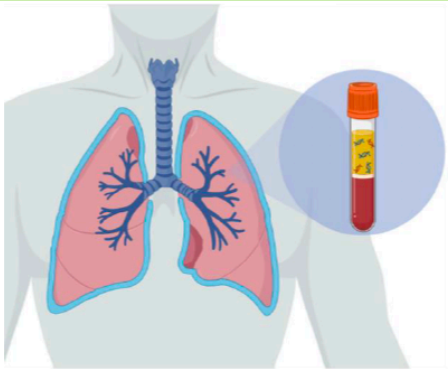
- NADIM showed **positive results in terms of survival**, **OS rate** at 36 months of **81.9% in the ITT** population rising to **91.0% in the PP** population with a 94% data maturity.
- **PFS** at 36 months **was 69.6% and 81.1% in the ITT and PP** population, respectively.
- Survival time was almost three times that reported in historical series, in which the 3-year OS did not exceed 30%.
- In an exploratory analysis, **clinical responses** based on CT-scans and according to RECIST v1.1 criteria **did not predict survival** outcomes. However, in the multivariate analysis, pathological complete response **(pCR) or undetectable ctDNA levels after neoadjuvant** treatment significantly **predicted long-term survival**

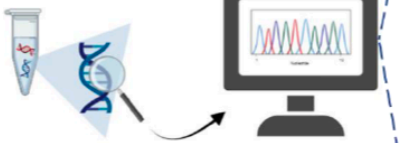
Provencio M, et al OA20.01

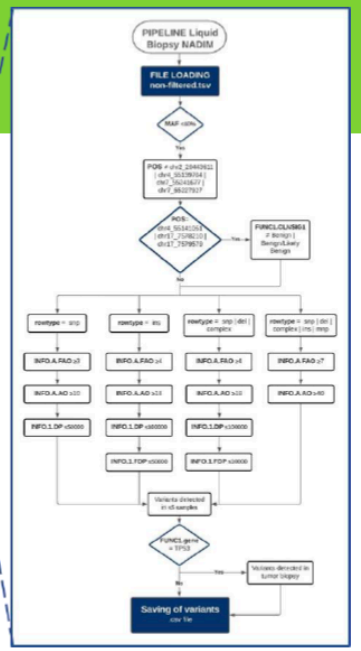
Pre-treatment levels of ctDNA for long-term survival prediction in stage IIIA NSCLC treated with neoadjuvant chemo-immunotherapy

METHODS









For biomarker analysis, data from patients who died from COVID19 (N=2) were excluded as these patients did not show progression disease according to CT-scans during the study

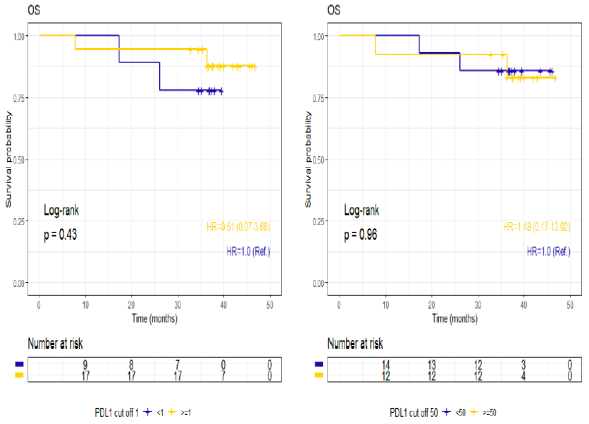
Romero A, et al. OA 20.02

➢ The expression of PD-L1 in tumor cells was not associated with improved PFS or OS.

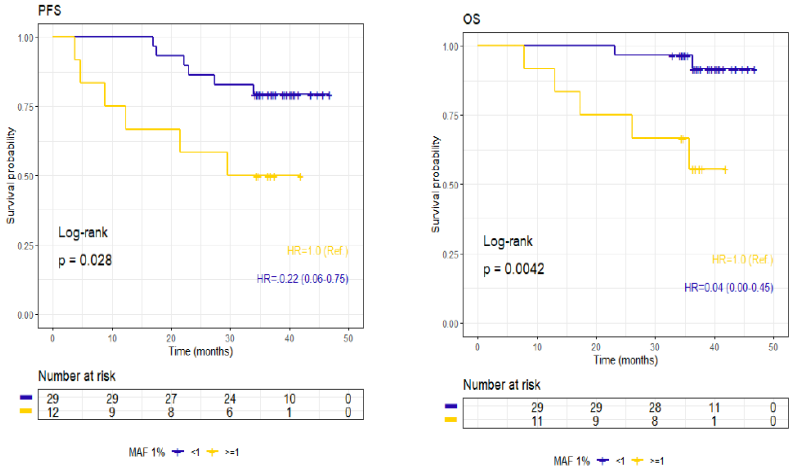
		Survival function at 36months		Hazard ratio (95% CI)[a]	P Value[a]
		Below cut-off	*Above or equal cut-off*		
PFS	PDL1 cutoff 1%	0.67	0.72	0.78 (0.18-3.29)	NS
	PDL1 cutoff 50%	0.71	0.69	1.10 (0.25-4.79)	NS
OS	PDL1 cutoff 1%	0.78	0.94	0.51 (0.07-3.68)	NS
	PDL1 cutoff 50%	0.86	0.92	1.48 (0.17-13.02)	NS

CI: Confidence Interval

PD-L1 was also evaluated as a continuous variable and no significant association was found (P=0.696 and P=0.660 for PFS and OS, respectively)



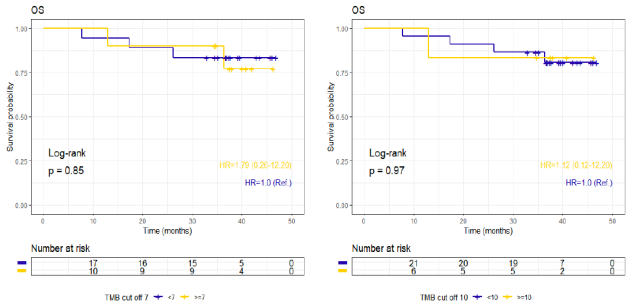
Pre-treatment ctDNA levels



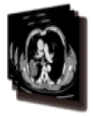
➢ TMB assessment as measured by the commercial pipeline was not associated with survival outcomes

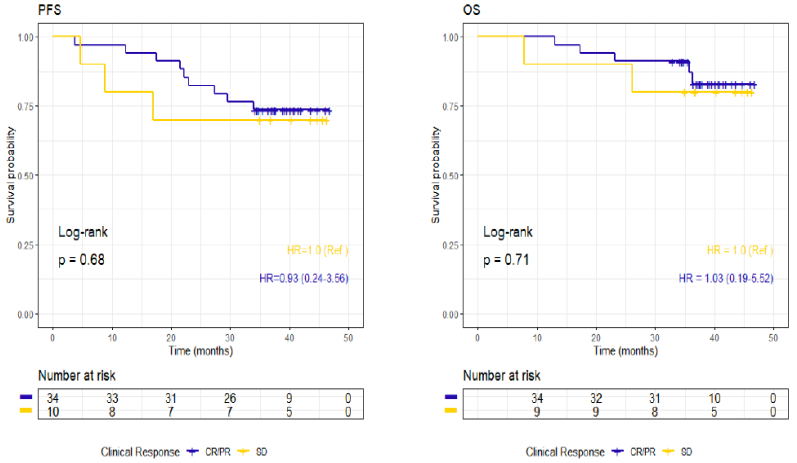
		Survival function at 36 months		Hazard ratio (95% CI)[a]	P Value[a]
		Below cut-off	*Above or equal cut-off*		
PFS	TMB as a continuous variable			0.98 (0.91-1.06)	NS
	TMB cutoff 7 mut/Mb	0.67	0.70	1.06 (0.24-4.63)	NS
	TMB cutoff 10 mut/Mb	0.68	0.67	1.31 (0.26-6.60)	NS
	TMB cutoff 16 mut/Mb	0.70	0.60	1.73 (0.34-8.67)	NS
OS	TMB as a continuous variable			0.99 (0.91-1.08)	NS
	TMB cutoff 7 mut/Mb	0.83	0.90	1.79 (0.26-12.20)	NS
	TMB cutoff 10 mut/Mb	0.86	0.83	1.12 (0.12-10.47)	NS
	TMB cutoff 16 mut/Mb	0.87	0.80	1.37 (0.15-12.81)	NS

CI: Confidence Interval; mut: mutations.



Clinical response ascertained on CT-scans



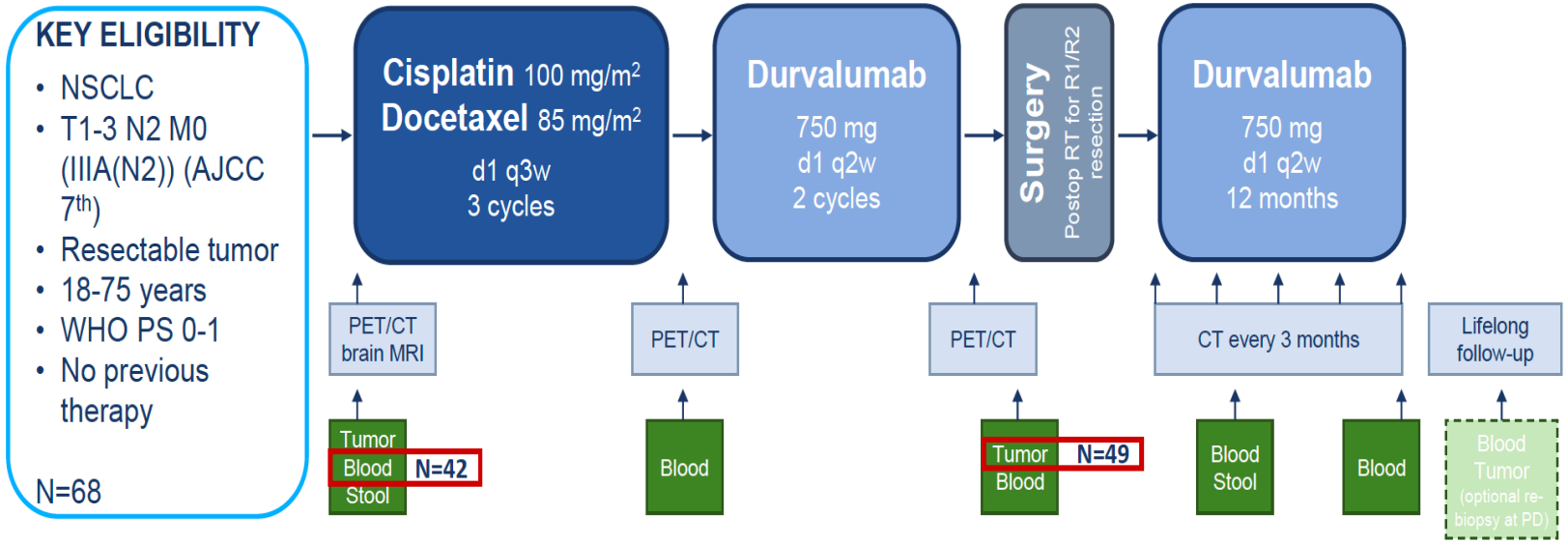


- **Neither TMB nor PDL1** were predictive for long-term survival in NADIM trial.
- Pre-treatment circulating tumor DNA analysis can identify patients at high risk of progression and out performed radiological response assessed according to RECIST criteria v1.1 in the prediction of survival

Atocha romero OA 20.02

SAKK 16/14 -T-cell receptor repertoire metrics predict response to neoadjuvant durvalumabin patients with stage IIIA(N2) NSCLC

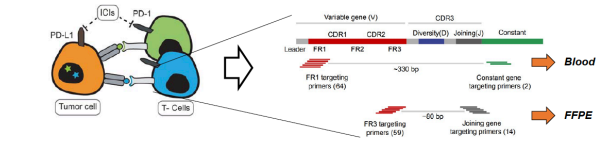
SAKK 16/14 – Study Design



1° endpoint: Event-free survival (EFS) at 12 months

2° endpoints: EFS, OS, ORR, pCR, MPR, nodal downstaging, complete resection, AEs

TCR-beta repertoire sequencing using Oncomine™ TCR-beta Assay



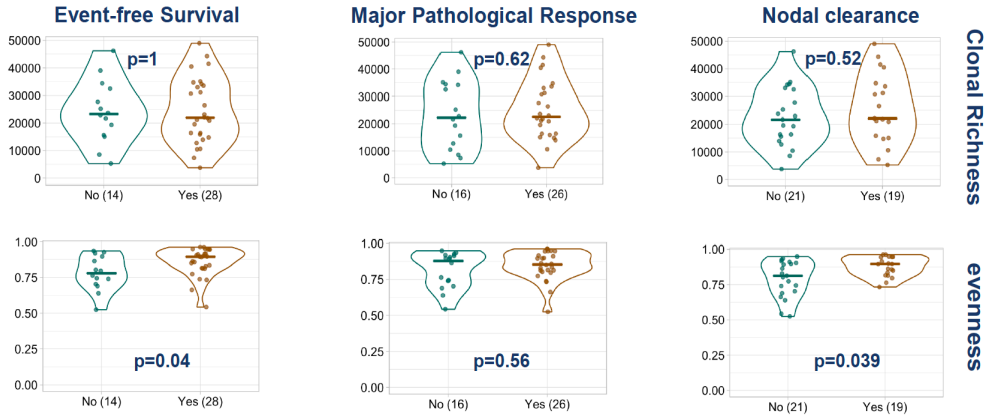
Clonal Richness= Total number of observed clones

Shannon Diversity = Measurement of the clonal diversity of a repertoire. Samples having many clones of similar frequencies will have a high Shannon Diversity

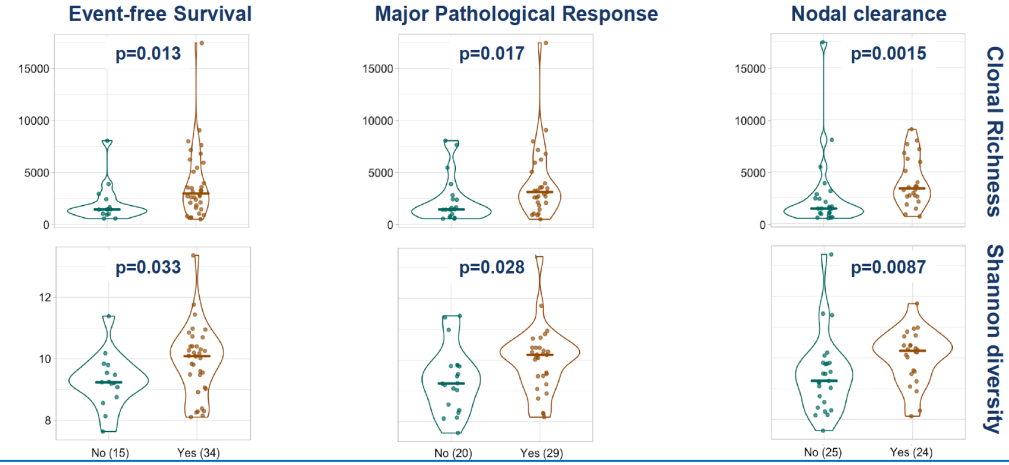
Evenness= Measurement of the similarity of clone sizes within the population.

Rotheschild S, et al. MA09.02

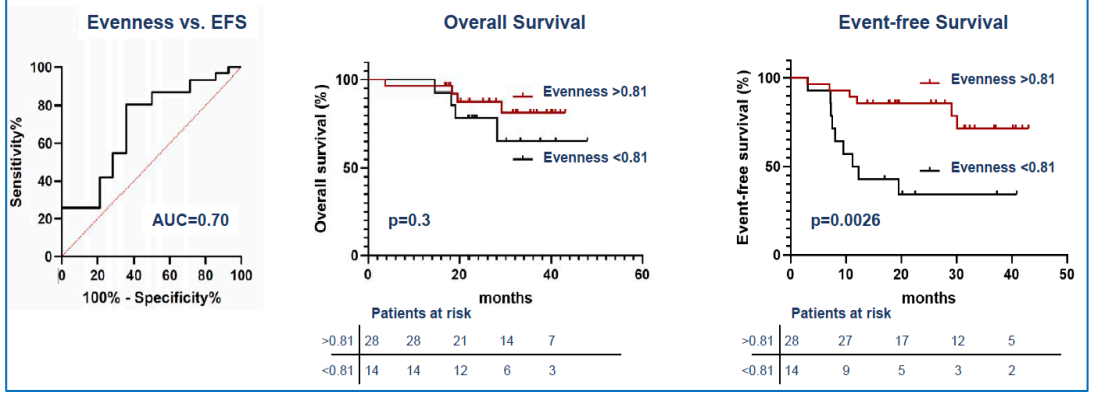
Baseline peripheral blood TCR repertoire



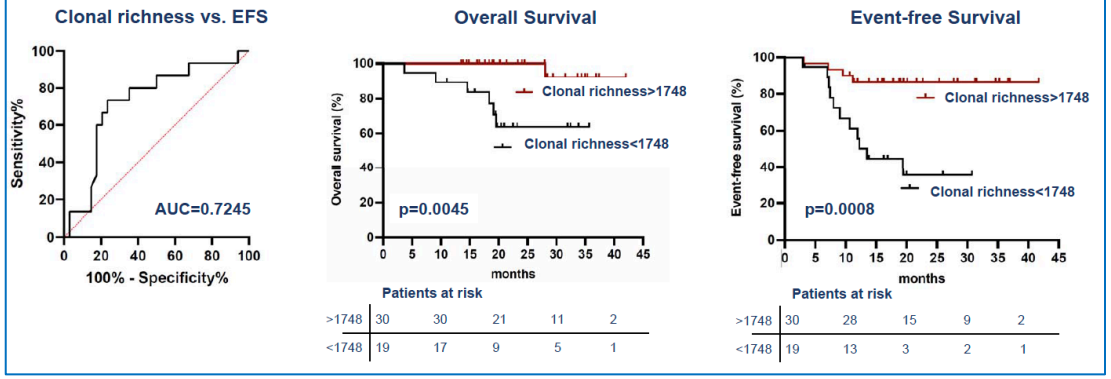
Post-treatment tumor tissue TCR repertoire



Baseline peripheral blood TCR repertoire



Post-treatment tumor tissue TCR repertoire

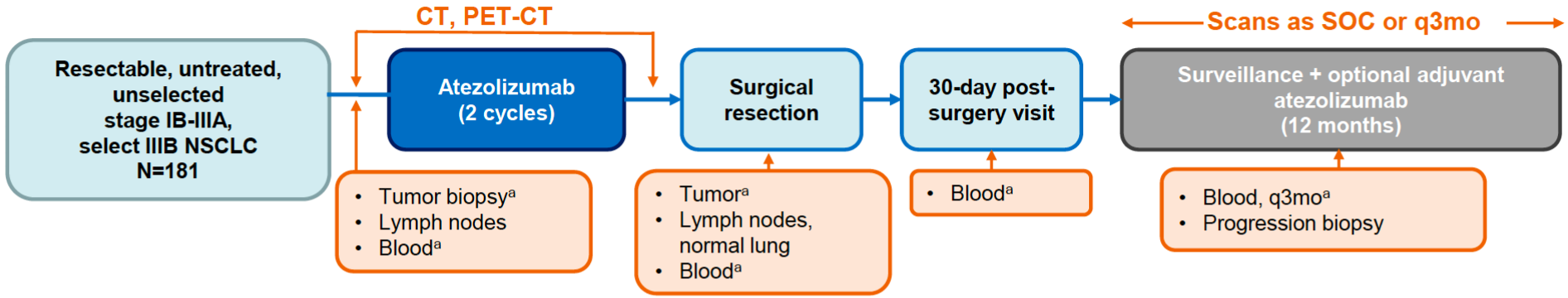


- TCR repertoire measured in peripheral blood samples and tumor tissue may provide a useful tool for predicting risk of recurrence after neoadjuvant sequential chemo-immunotherapy with durvalumab in patients with resectable stage IIIA(N2) NSCLC
- **Baseline peripheral blood TCR repertoire is associated with EFS and nodal clearance, but not MPR**
- **Post-treatment tumor tissue TCR repertoire is associated with EFS, MPR, and nodal clearance**
- **TMB in post-treatment tumor tissue is not associated with EFS, MPR, or nodal clearance**

Rotheschild S, et al. MA09.02

LCMC3: Immune Cell Subtypes Predict Pathologic Response After Neoadjuvant Atezolizumab in Resectable NSCLC

LCMC3 study design



Primary endpoint:

- MPR (≤10% viable tumor cells)

Exploratory endpoints:

- Biomarkers: flow cytometry, scRNAseq, bulk RNAseq, TCRseq

- LCMC3 is the largest reported study of anti–PD-L1 neoadjuvant therapy conducted to date (n=181)
- We explored whether the peripheral blood immunophenotype assessed via 10-color 60-marker flow cytometry and the tumor microenvironment (TME) assessed via RNAseq would be predictive of MPR
  - Comprehensive immunophenotyping via 10-color 60-marker IMMUNOME flow cytometry of peripheral blood at baseline
  - Tumor scRNAseq data (n=13) and tumor bulk RNAseq data from pre- (n=56) and post-treatment (n=44) samples

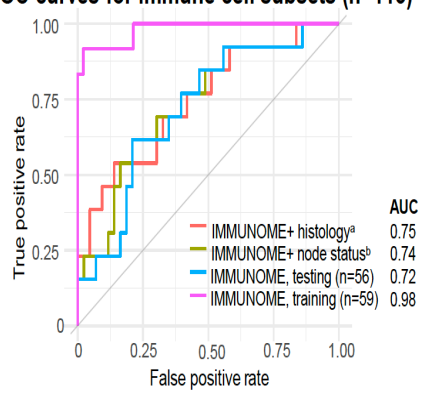
CT, computed tomography; MPR, major pathological response; NSCLC, non-small cell lung cancer; PET, positron emission tomography; q3mo, every 3 months; RNAseq, RNA sequencing; scRNAseq, single-cell RNA sequencing; SOC, standard of care; TCRseq, T-cell receptor sequencing.

[a] Mandatory. NCT02927301

Oezkan F, et al. MA09.01

Baseline peripheral blood immunophenotypes predict MPR

ROC curves for immune cell subsets (n=115)



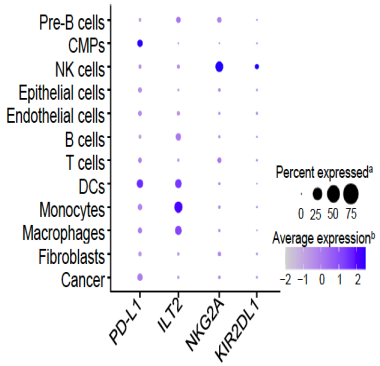
	Cell type	CD45⁺ immunophenotype
Positively associated with MPR	Non-T/ non-NK cells	**ILT2⁺NKG2A⁻**CD63⁻CD3⁻CD158e1⁻CD158b⁺CD56⁻**KIR2DL1⁺**CD16⁻
		NKG2A⁻CD94⁻NKG2D⁺CD3⁻CD56⁻CD117⁻CD127⁻CD161⁻CD16⁻
	NK cell	**NKG2A⁺**HLA-DR⁺CD69⁺CD3⁻CD158e1⁻CD158b⁻CD56⁻**KIR2DL1⁻**CD16⁺
Negatively associated with MPR	NK cells	CD16⁺CD336⁻CD3⁻CD244⁻CD335⁺NKG2D⁻CD56⁻CD161⁻CD337⁺
		ILT2⁺NKG2A⁺CD63⁻CD3⁻CD158e1⁻CD158b⁻CD56⁺**KIR2DL1⁻**CD16⁻
	NK-like T cells	**NKG2A⁺**HLA-DR⁻CD69⁺CD3⁺CD158e1⁻CD158b⁻CD56⁺**KIR2DL1⁻**CD16⁻
		HLA-DR⁺CD69⁻CD19⁻CD56⁺CD16⁻CD134⁻CD4⁻CD3⁺CD8⁺
		NKG2A⁻CD94⁻NKG2D⁺CD3⁺CD56⁺CD117⁻ CD127⁻CD161⁻CD16⁺
		ILT2⁺NKG2A⁺CD63⁻CD3⁺CD158e1⁻CD158b⁻CD56⁺**KIR2DL1⁻**CD16⁻
		γ/δ⁻α/β⁺CD19⁻CD56⁺CD16⁻CD13/14⁻CD4⁺CD3⁺CD8⁺
		γ/δ⁺α/β⁻CD19⁻CD56⁺CD16⁺CD13/14⁻CD4⁻CD3⁺CD8⁻
		γ/δ⁻α/β⁻CD19⁻CD56⁺CD16⁺CD13/14⁻CD4⁻CD3⁺CD8⁻
	Naive T cell	CD62⁻CD27⁺CD56/16⁻CD45RO⁻CCR7⁻CD45RA⁺CD4⁺CD3⁺CD8⁺

- IMMUNOME flow cytometry data from pre-treatment peripheral blood samples (n=115) were used to build an immune cell model predictive of MPR
- The algorithm was informed by 13 samples each from patients with ≥88% viable tumor cells and patients with ≤20% viable tumor cells at surgery
- Pre-treatment peripheral blood samples were placed into training or testing sets and analyzed using an approach based on generalized additive models and regularized regression (LASSO). Immune cell subsets detected in fewer than 50% of samples were excluded
- 13 immune cell subsets in the baseline peripheral blood sample predicted MPR, including NK-cell and NK-like T-cell subtypes expressing ILT2 and NKG2A

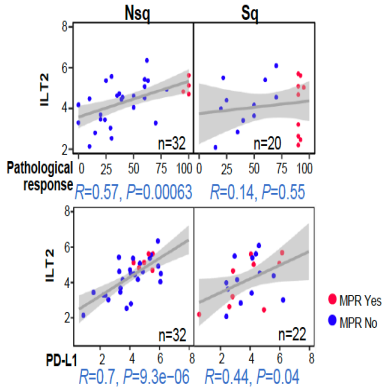
AUC, area under the curve; LASSO, least absolute shrinkage and selection operator; MPR, major pathological response; NK, natural killer; ROC, receiver operating curve.
[a] Non-squamous vs squamous. [b] N1/N2 vs N0.

TME analysis showed innate immune markers were associated with MPR

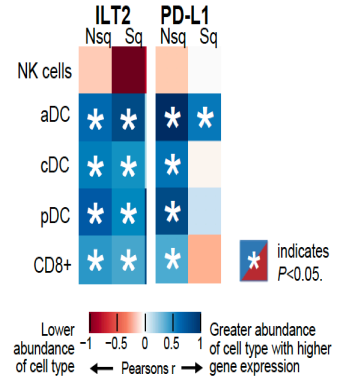
scRNA sequencing of 13 tumors at surgery for IMMUNOME markers



Bulk RNA sequencing of tumor at baseline (n=56)



Inhibitory signaling association with cell types at baseline



- TME scRNAseq data showed high ILT2 expression on macrophages, monocytes and DCs, and high PD-L1 expression on DCs; NKG2A and KIR2DL1 were mostly expressed on NK cells
- Bulk RNAseq data at baseline revealed significantly more ILT2 expression in MPR patients and a linear correlation between ILT2 and PD-L1 expression in the TME, suggesting a co-expression of ILT2 and PD-L1 on the same cells
- By bulk RNAseq, PD-L1 and ILT2 expression were both positively associated with the abundance of DCs and CD8⁺ T cells

aDC, activated dendritic, cell; cDC, conventional dendritic cell; CMP, common myeloid progenitor cell; DC, dendritic cell; MPR, major pathological response; NK, natural killer; Nsq, non-squamous; pDC, plasmacytoid dendritic cell; scRNAseq, single-cell RNA sequencing; Sq, squamous; TME, tumor microenvironment. [a] Dot size represents percentage of NK cells in the group expressing the gene. [b] Color represents scaled average normalized expression.

- MPR may be predicted by innate immune markers assessed via 10-color 60-marker IMMUNOME flow cytometry in pre-treatment peripheral blood
- Innate immune cells including ILT2-and NKG2A-expressing NK cells and NK-like T cells in the peripheral blood were associated with the anti-cancer immune response to treatment with neoadjuvant atezolizumab
- Tumor RNAseq data revealed a positive association of ILT2 expression with MPR, which is mostly expressed on dendritic cells, macrophages and monocytes and linearly associated with PD-L1 expression, suggesting co-expression of ILT2 and PD-L1 on the same cells

UNRESECTABLE STAGE III DISEASE

PATTERNS OF CARE IN MAINTENANCE THERAPY IN U.S. PATIENTS UNDERGOING DEFINITIVE CHEMORADIATION FOR STAGE 3 NSCLC

- Utilizes RWD from IQVIA
  - Open claims
    - N=8071 patients with NSCLC included
    - N=1794 (22.2%) received maintenance durvalumab after chemoRT
    - Among durvalumab non-recipients (N=6277)
      - 2785 (34.5%) received maintenance chemo
      - 2047 (25.4%) received maintenance pembrolizumab
      - 2820 (34.9%) received no maintenance therapy
  - Closed claims
    - N=357 patients with NSCLC included
    - N=127 (35.6%) received maintenance durvalumab after chemoRT
    - Among durvalumab non-recipients (N=230)
      - 124 (34.7%) received maintenance chemo
      - 82 (23.0%) received maintenance pembrolizumab
      - 72 (20.2%) received no maintenance therapy

TREATMENT RECOMMENDATIONS FOR STAGE III NSCLC BY 3 DUTCH MULTIDISCIPLINARY TUMOR BOARDS PRIOR TO, AND FOLLOWING THE PACIFIC TRIAL

Patients and methods

- Patients presenting with stage III NSCLC from 2015 – 2019
- 3 regional thoracic MDT's, comprising 7 Dutch hospitals
- Radical intent treatments (RIT) defined as either

  (i) CCRT or

  (ii) multi-modality schemes incorporating planned surgery

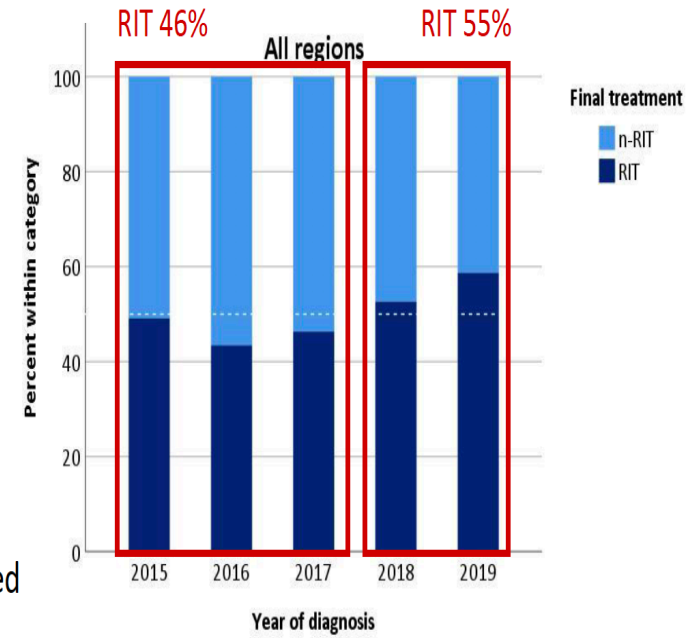
Ronden M, et al. MA06.06

Key Results (1)

- 855 patients presented with stage III NSCLC between 2015-2019
- 95% were discussed at a thoracic MDT

- RIT recommended by the MDT in 63%
  - 47% CCRT, 16% surgery
- 52% of patients finally received a RIT
  - 38% CCRT, 13% surgery

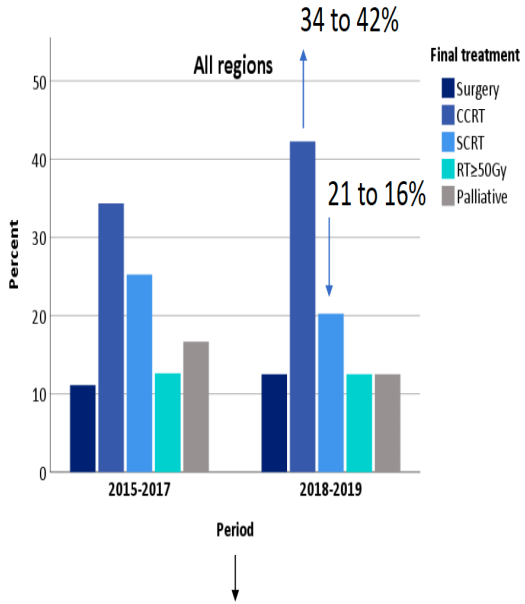
- Since 2018, 57% of patients who completed CCRT, commenced durvalumab treatment



Key Results (2)

Predictors for not undergoing a RIT

- Age ≥70 years
- WHO performance score ≥2
- Charlson Comorbidity Index ≥2 (excluding age)
- FEV1<80% of predicted value
- N3-disease
- Period of diagnosis



Early toxicity and early mortality comparable!

- Changes in treatment recommendations by MDT's after 2018 when results of the PACIFIC trial became available, with more patients undergoing CCRT
- In the real world setting, only 50% of patients with stage III NSCLC were fit to undergo radical intent treatments (RIT)
- The findings highlight the unmet needs of patients who are unfit for RIT (CCRT, surgery)

Challenges in Delivery of Curative-Intent CCRT

Diagnosis and Staging	Timely access to tests/results	• Education to referring doctors • Nurse navigation • Central scheduling
Treatment Planning	Optimal treatment strategy	• Multidisciplinary tumor board
Chemoradiation: Initiation and management	Access in distant areas Monitoring of AEs	• Social work, resources, transport • Close monitoring, early management of toxicity
Immunotherapy: Initiation and management	Multidisciplinary management irAEs Financial toxicity	• Early discussion of durvalumab • Dosing schedules • Patient Education

Brade et all, Current Oncology, 2021

GRACIAS